Table 4 The result of gene ontology analysis of valproate

Term	Count	Fold enrichment	*P* value	Bonferroni
Biological process				
GO:0044237 ~ cellular metabolic process	231	1.27	5.28E−08	2.78E−04
GO:0043170 ~ macromolecule metabolic process	208	1.31	7.09E−08	3.73E−04
GO:0008152 ~ metabolic process	249	1.23	8.62E−08	4.53E−04
GO:0044238 ~ primary metabolic process	229	1.25	2.38E−07	1.25E−03
GO:0043283 ~ biopolymer metabolic process	163	1.38	4.28E−07	2.25E−03
GO:0007049 ~ cell cycle	45	2.28	4.40E−07	2.31E−03
GO:0009987 ~ cellular process	315	1.10	1.64E−06	8.57E−03
GO:0006139 ~ nucleobase, nucleoside, nucleotide and nucleic acid metabolic process	128	1.43	3.31E−06	1.72E−02
GO:0016043 ~ cellular component organization and biogenesis	94	1.56	4.43E−06	2.30E−02
GO:0051649 ~ establishment of cellular localization	42	2.16	4.60E−06	2.39E−02
GO:0051641 ~ cellular localization	42	2.10	9.04E−06	4.64E−02
Cellular component				
GO:0005622 ~ intracellular	313	1.38	2.86E−28	2.48E−25
GO:0044424 ~ intracellular part	306	1.43	4.32E−30	3.75E−27
GO:0043229 ~ intracellular organelle	264	1.48	6.19E−22	5.37E−19
GO:0043226 ~ organelle	264	1.48	6.76E−22	5.87E−19
GO:0043231 ~ intracellular membrane-bound organelle	241	1.55	2.11E−21	1.83E−18
GO:0043227 ~ membrane-bound organelle	241	1.55	2.25E−21	1.96E−18
GO:0005737 ~ cytoplasm	216	1.61	1.49E−19	1.29E−16
GO:0044444 ~ cytoplasmic part	133	1.66	1.41E−10	1.22E−07
GO:0044446 ~ intracellular organelle part	126	1.67	4.13E−10	3.59E−07
GO:0044422 ~ organelle part	126	1.66	5.10E−10	4.42E−07
GO:0005634 ~ nucleus	152	1.51	2.92E−09	2.53E−06
GO:0032991 ~ macromolecular complex	97	1.72	2.95E−08	2.56E−05
GO:0044428 ~ nuclear part	48	2.10	1.77E−06	1.54E−03
GO:0043234 ~ protein complex	77	1.69	3.30E−06	2.86E−03
GO:0005739 ~ mitochondrion	43	2.07	9.83E−06	8.50E−03
GO:0044464 ~ cell part	338	1.04	5.37E−05	4.56E−02
GO:0005623 ~ cell	338	1.04	5.47E−05	4.64E−02
Molecular function				
GO:0003676 ~ nucleic acid binding	119	1.54	2.51E−07	7.22E−04
GO:0005515 ~ protein binding	233	1.54	6.13E−19	1.76E−15
GO:0005488 ~ binding	313	1.15	4.54E−08	1.31E−04
GO:0003677 ~ DNA binding	82	1.60	1.19E−05	3.37E−02

rigorously analyzed the microarray data, the results may contain false positives, and thus need to be confirmed by independent technologies.

Conclusion

In summary, we performed a comprehensive DNA microarray analysis to examine gene expression profiles in LCs exposed to lithium or valproate. Lithium and valproate had distinctive effects on gene expression in the LCs, suggesting that different molecular mechanisms are involved in the mechanism of action of these two mood stabilizers. Among the genes commonly altered by lithium and valproate, *VEGFA* was the gene most downregulated by both drugs. The mechanisms of action of these mood stabilizers may be mediated in part by their effects on *VEGFA* in non-neuronal cells, and *VEGFA* may therefore be useful as a peripheral marker of the effects of mood stabilizers.

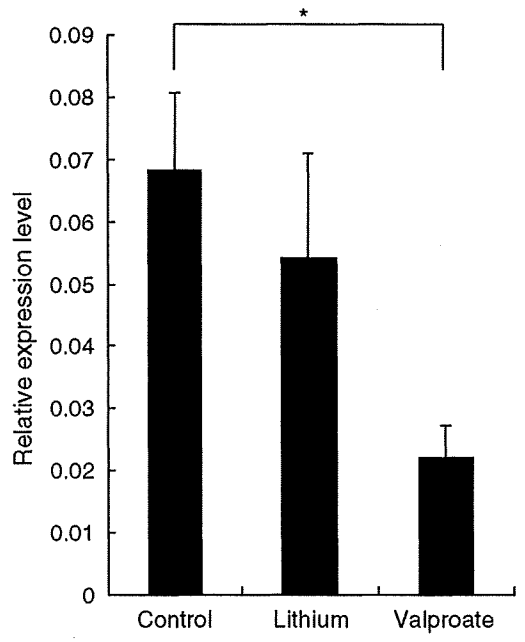

Fig. 2 The results of real-time quantitative RT-PCR. The expression level (mean ± SD) of *VEGFA* in control, lithium-treated, and valproate-treated LCs. $*P < 0.05$

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Anti-Inflammatory Effects of Antidepressants: Possibilities for Preventives Against Alzheimer's Disease

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Abstract: Increasing evidence of pro-inflammatory mediator expression in major depressions indicate that inflammatory changes may play a role. If this is true, the efficacy of antidepressants may be partially attributable to suppression of inflammation. Various types of antidepressants can suppress serum and plasma levels of pro-inflammatory mediators in patients with major depression. Therefore they can inhibit the production of pro-inflammatory mediators by immune cells. These include glial cells, which are the main sources and targets of cytokines in the brain. This review summarizes the evidence showing that antidepressants have an anti-inflammatory potential. The putative mechanisms are also discussed. Because of the anti-inflammatory effects of antidepressants, they might also act as preventives for neurodegenerative dementias including Alzheimer's disease, where the pathogenesis involves chronic inflammation associated with activated microglia.

Keywords: Antidepressants, major depression, Alzheimer's disease, inflammation, cytokines, microglia.

INTRODUCTION

The history of antidepressant drug development has been unique and fortuitous. The monoamine oxidase inhibitor iproniazid and the tricyclic antidepressant (TCA) imipramine were originally developed as a tuberculosis remedy and as an antihistamine, respectively [1]. These drugs were serendipitously found to have an antidepressant effect in the 1950s, and soon thereafter were shown to increase synaptic levels of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) [1]. Currently, it has been shown that antidepressants modulate not only the monoamine neurotransmitter system but also the inflammatory system.

The association between inflammation and major depression has been supported by the well-known observation that pro-inflammatory cytokines such as interferon (IFN)-α, which is used to treat patients with hepatitis C, and interleukin (IL)-2, which is used to treat patients with certain cancers, frequently induce depressive symptoms as side effects. In addition, depression is often found in inflammatory diseases such as multiple sclerosis, allergies of different types, and rheumatoid arthritis, in which pro-inflammatory cytokines are over-expressed [2]. Animal studies also support this idea. Chronic administration of the endotoxin lipopolysaccharide (LPS) or pro-inflammatory cytokines into rats has been shown to induce symptoms similar to depression. These symptoms are referred to as sickness behavior, which includes appetite loss, suppressed sexual behavior and apathy [3, 4].

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It can be hypothesized that if inflammation plays a causative role in the pathogenesis of major depression, antidepressants may partially act by suppressing such inflammation. The first evidence indicating that antidepressants have anti-inflammatory effects appeared four decades ago. Martelli *et al.* (1967) showed that administration of TCAs inhibited chemically induced edema in the standard rat paw assay [5]. Ten years later, Horrobin and colleagues reported that the TCA clomipramine was a powerful antagonist of prostaglandin (PG) E_2 [6] and then proposed that diverse antidepressants are inhibitors of PG synthesis [7]. In fact, a recent *in vitro* study revealed that the selective serotonin reuptake inhibitor (SSRI) paroxetine attenuated cyclooxygenase (COX)-2 expression in human T cells stimulated with phytohemagglutinin (PHA) [8]. Furthermore, experimental evidence is accumulating that various types of antidepressants exert anti-inflammatory effects by decreasing pro-inflammatory cytokine levels or increasing anti-inflammatory cytokine levels.

This review focuses on the influence of antidepressants on inflammatory mediator levels, particularly serum and plasma cytokine levels, in depressed patients. It also focuses on glial production of those mediators *in vitro* since glial cells are the major immune cells responsible for inflammation in the brain. We also discuss possible mechanisms of the anti-inflammatory action of antidepressants and the potential of antidepressants to act as preventives against Alzheimer's disease (AD).

EVIDENCE FOR INFLAMMATION ASSOCIATED WITH MAJOR DEPRESSION

It has been reported that the levels of acute phase proteins such as C-reactive proteins (CRP), α2-macroglobulin, α1-acid glycoprotein, complement C4 and haptoglobin are

upregulated in major depression [9-14]. The levels of PGE_2 and thromboxane B_2 are also reported to be elevated in depressed patients [15-17]. Moreover, major depression is accompanied by increased levels of pro-inflammatory cytokines such as IL-1β, IL-6, IFN-γ and tumor necrosis factor (TNF)-α [18-23] whereas the anti-inflammatory cytokine transforming growth factor (TGF)-β1 has been shown to be decreased [24].

In contrast to many studies on serum and plasma levels, there have been few on cerebrospinal fluid (CSF) levels. Only IL-1β has been shown to be increased in major depression [25] while IL-6 was decreased [25] or not changed [26] and TNF-α was not changed [25].

It is uncertain whether inflammation is a cause or a result of major depression. In addition, it must be noted that not all studies have found such an association [27, 28]. Nevertheless, inflammation certainly appears to be a factor in at least some cases of major depression. Indeed, Müller *et al.* (2006) have recently shown interesting data that depressed patients treated for 6 weeks with the serotonin-noradrenaline reuptake inhibitor (SNRI) reboxetine plus the COX 2 inhibitor celecoxib showed significantly greater improvement in scores on the Hamilton Depression Scale compared to the reboxetine-alone group [29].

EFFECT OF ANTIDEPRESSANTS ON INFLAMMATORY MEDIATOR LEVELS IN PATIENTS WITH MAJOR DEPRESSION

Several groups have studied serum or plasma levels of various cytokines and their receptors in patients with major depression before and after antidepressant pharmacotherapy (Table **1**, for a summery of studies before 2000 see [30]). Tuglu *et al.* (2003) showed that administration of SSRIs for 6 weeks decreased serum levels of TNF-α and CRP [23]. Basterzi *et al.* (2005) showed that similar SSRI treatment diminished serum IL-6 levels [31]. In keeping with such an anti-inflammatory effect, Myint *et al.* (2005) reported that 8-weeks of antidepressant treatment increased plasma TGF-β1 levels [24]. Interestingly, it has been shown that plasma levels of TNF-α and IL-6 in patients with SSRI-resistant depression are significantly higher than those in healthy controls [32]. However, Kubera *et al.* (2000) demonstrated that a 6-week antidepressant treatment which elicited successful clinical remissions did not change significantly the serum levels of IL-6, IL-10 and IL-1 receptor antagonist [33]. Two studies even described increases in the plasma TNF-α levels following antidepressant treatment. Kraus *et al.* (2002) reported that a 4-week treatment with a tetracyclic antidepressant (i.e., mirtazapine) increased the plasma levels of TNF-α and soluble TNF-α receptors significantly while a similar treatment with the SNRI venlafaxine did not influence those levels [34]. Kagaya *et al.* (2001) showed that plasma TNF-α level was increased after 1-month pharmacotherapy consisting mainly of clomipramine. They also examined the plasma levels of IL-1β and IL-6. Those levels after treatment were lower than before treatment, but not significantly [35].

Taken together, the effect of antidepressants on serum and plasma levels of inflammatory cytokines in depressed patients is still controversial. Such an inconsistency may stem from the difference in methodology employed and the limitation due to the small numbers tested in these clinical studies (e.g., n<30 in each study). In addition, Kennis and Maes (2002) pointed out the technical difficulty in detecting serum and plasma levels of cytokines since circulating cytokine levels are very low in human subjects [30]. Therefore, early studies on the cytokine concentrations before and after antidepressant treatment often employed *ex vivo* methods. Specifically, cytokine levels in the supernatants of cultured whole blood or cultured peripheral blood mononuclear cells (PBMCs) from depressed patients were measured by enzyme-linked immunosorbent assay (ELISA). In both cases, cytokine production was induced by stimulation with LPS and/or mitogens such as PHA and concanavalin A. Such *ex vivo* studies have shown inconsistent results on protein levels (for review see [30]).

Recently, Tsao *et al.* (2006) examined mRNA expression of inflammatory cytokines in non-stimulated PBMCs from depressed patients before and after 3-month SSRI (i.e., fluoxetine) treatment by using reverse transcriptase-polymerase chain reaction (RT-PCR) assy. They found that such pharmacotherapy significantly diminished the mRNA expression of IFN-γ. The mRNA expressions of IL-1β and TNF-α were also inhibited, but not significantly [36].

EFFECT OF ANTIDEPRESSANTS ON GLIAL PRODUCTION OF INFLAMMATORY MEDIATORS *IN VITRO*

With regard to *in vitro* studies, various types of antidepressants have anti-inflammatory effects in terms of cytokine production by immune cells. Early studies focused on the effects of antidepressants on cytokine production by cultured PBMCs or cultured whole blood from healthy subjects or depressed patients. They demonstrated that *in vitro* treatment with various types of antidepressants decreased the production of pro-inflammatory cytokines including IFN-γ while increasing the production of such anti-inflammatory cytokines as IL-10 (for reviews see [30, 37]). Moreover, a TCA (amitriptyline) and a SSRI (fluoxetine) were shown to attenuate the production of pro-inflammatory cytokine-induced PGE_2 and nitric oxide (NO) by cultured human synovial cells [38].

Increasing evidence strongly suggests that changes in cytokine levels outside the brain cause changes in cytokine expression and activity in the brain, and *vice versa* [39]. In other words, the central and peripheral cytokine compartments are integrated but differently regulated [40]. In the brain, microglia and astrocytes are the major cell types that participate in the inflammatory system both as sources and targets of cytokines. This fact suggests that these glial cells may represent overlooked targets in the etiology of major depression. Several studies have recently investigated the effects of antidepressants on the glial production of inflammatory mediators *in vitro* (Table **2**).

Obuchowicz *et al.* (2006) examined the effects of amitriptyline and its metabolite nortriptyline on the production of IL-1β and TNF-α by rat microglial and mixed glial (i.e., microglia plus astrocytes) cultures stimulated with LPS, using both ELISA and quantitative RT-PCR. They found

Table 1. Summary of Studies on Serum/Plasma Levels of Inflammatory Mediators in Depressed Patients Before and After Antidepressant Therapy

Study	n	Antidepressants	Target Studied	Result
Tuglu *et al.* (2003)	26	SSRIs (mostly Sertraline/Citalopram)	TNF-α	Decrease
			CRP	Decrease
Basterzi *et al.* (2005)	23	SSRIs (not specified)	IL-6	Decrease
Myint *et al.* (2005)	10	Various types (mostly Paroxetine/Fluoxetine)	TGF-β1	Increase
Kubera *et al.* (2000)	9	Not specified	IL-6	No change
			IL-10	No change
			IL-1RA	No change
Kraus *et al.* (2002)	9	SNRI (Venlafaxine)	TNF-α	No change
			sTNF-Rs	No change
	11	Tetracyclic (Mirtazapine)	TNF-α	Increase
			sTNF-Rs	Increase
Kagaya *et al.* (2001)	12	Mostly TCA (Clomipramine)	TNF-α	Increase
			IL-1β	No change
			IL-6	No change

IL-1RA, IL-1 receptor antagonist
sTNF-Rs, soluble TNF receptors

Table 2. Summary of Studies that Examined the Effect of Antidepressants on Glial Production of Inflammatory Mediators *In Vitro*

Study	Cell Used	Antidepressants	Target Studied	Result
Obuchowicz *et al.* (2006)	Rat microglia Rat mixed glia	TCAs (Amitriptyline/Nortriptyline)	IL-1β	Decrease
			TNF-α	Decrease
			IL-1β mRNA	No change
			TNF-α mRNA	No change
Hashioka *et al.* (2007)	Mouse microglia (6-3)	TCA (Imipramine)	IL-6	Decrease
			NO	Decrease
		SSRI (Fluvoxamine)	IL-6	Decrease
			NO	Decrease
		SNRI (Reboxetine)	IL-6	Decrease
			NO	Decrease
		LiCl	IL-6	Increase
			NO	Decrease
Vollmar *et al.* (2008)	Rat mixed glia	SNRI (Venlafaxine)	IL-6	Decrease
			IFN-γ	Decrease
			TGF-β	Increase
			IL-10	No change

(Table 2) contd....

Study	Cell Used	Antidepressants	Target Studied	Result
Ha *et al.* (2006)	Mouse microglia (BV2)	SSRI (Fluoxetine)	NO	Increase
			iNOS mRNA	Increase
			IL-6 mRNA	Increase
			TNF-α mRNA	Increase
			NF-κB activity	Increase

that treatment with those antidepressants for 24 h significantly inhibited the secretion of both cytokines, but did not change the expression of the mRNAs [41].

We previously studied the effects of various types of antidepressants, as well as the mood stabilizer lithium chloride, on the release of the pro-inflammatory mediators IL-6 and NO from IFN-γ-activated murine 6-3 microglial cells by using ELISA and the Griess reaction, respectively [42]. We showed that 24-h pretreatment with the TCA imipramine, the SSRI fluvoxamine or the SNRI reboxetine significantly inhibited IL-6 and NO production in a dose-dependent manner. On the other hand, lithium chloride had a different spectrum of action, namely by enhancing IFN-γ-induced IL-6 production and inhibiting NO production.

Vollmar *et al.* (2008) measured IL-6, IL-10, IFN-γ and TGF-β concentrations in an astroglia-microglia co-culture treated with venlafaxine for 16 h by ELISA assay [43]. The culture system they employed allows mimicking of an inflammatory milieu by increasing the cultured microglial fraction without any inflammatory stimuli. They demonstrated an augmentation of TGF-β release with a concomitant reduction in the secretion of IL-6 and IFN-γ. Furthermore, they found a significant change of microglial phenotype from activated to resting morphology.

In contrast to those studies, Ha *et al.* (2006) demonstrated that treatment of murine microglial BV_2 cells with fluoxetine resulted in significant increases in NO and in the mRNAs of inducible NO synthase (iNOS), IL-6 and TNF-α [44]. They furthermore showed that fluoxetine increased the DNA binding activity of transcription factor nuclear factor-κB (NF-κB), whose activation mediates inflammatory responses. However, the study did not measure the concentrations of IL-6 and TNF-α released from microglial cells. Based on this study and the study by Obuchowicz *et al.*, it can be presumed that antidepressants inhibit the glial secretion of pro-inflammatory cytokines but do not decrease their mRNA levels. Thus, antidepressants may induce post-transcriptional changes in pro-inflammatory cytokines or increase their degradation as Obuchowicz *et al.* suggested.

Although the majority of studies have shown that antidepressants of various classes decrease the glial production of pro-inflammatory cytokines and increase the anti-inflammatory cytokine production, the limitation of such *in vitro* studies should be addressed. Considering the fact that antidepressant treatment needs at least 10-14 days for any clinical effectiveness to appear, the treatment of glial cells with antidepressants for 16-24 h appear to reflect only acute effects of the drugs. In addition, we should note the antidepressant concentrations those studies employed. Maes *et al.* (1999) indicated that 1 μM corresponds to the plasma concentrations attained during clinical treatment [45]. Pharmacokinetic studies in animals have shown that the concentrations of antidepressants detected in certain organs such as the brain and spleen are 10-20 times higher than plasma concentrations due to the lipophilic property of antidepressants [46, 47]. Nevertheless, the concentrations 50-100 μM used in some *in vitro* studies seem to be rather higher than clinically relevant concentrations.

POSSIBLE MECHANISMS OF ANTI-INFLAMMATORY ACTIONS OF ANTIDEPRESSANTS

The exact mechanism by which antidepressants exert anti-inflammatory effects remains to be elucidated. Although one should remember the possible differences between the mechanism underlying anti-inflammatory effects of drugs *in vitro* and *in vivo*, several mechanisms are possible.

One of the most plausible involves an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. A number of *in vivo* studies have shown that many antidepressants increase intracellular concentrations of cAMP through activation of monoamine receptors such as the receptors for 5-HT and NA [48, 49]. Also, *in vitro*, data indicate that antidepressants of several classes increase intracellular cAMP levels [50, 51]. We demonstrated that TCA, SSRI and SNRI inhibited IFN-γ-induced microglial production of IL-6 and NO *in vitro*. These inhibitions were reversed by the cAMP inhibitor SQ 22536 and by the protein kinase A (PKA) inhibitor Rp-adenosine3', 5'-cyclic monophosphorothioate triethylammonium salt (Rp-3', 5'-cAMPS), suggesting that the anti-inflammatory effects of various antidepressants on microglia are at least partially mediated by the cAMP-dependent PKA pathway [42]. These results are consistent with findings in a study on human whole blood [52]. We also demonstrated that lithium chloride reduced IFN-γ-induced microglial production of NO. Interestingly, the inhibition by lithium chloride was not reversed by either SQ 22536 or Rp-3', 5'-cAMPS, indicating such an inhibitory effect of lithium chloride is not mediated by the cAMP/PKA pathway.

In a number of cell types, the activation of the cAMP/PKA pathway has been shown to inhibit NF-κB activity [53], whose activation is known to induce the gene expression of iNOS and various pro-inflammatory cytokines. Specifically, in rat primary astrocytes [54] and human monocytes [55], the activation of the cAMP/PKA pathway

inhibits LPS-mediated induction of NF-κB binding activity. Activation of the cAMP/PKA pathway not only down-regulates NF-κB activity, it also down-regulates the Janus family kinase (JAK)/signal transducer and activator of transcription (STAT) 1 pathway. Upregulation of the pathway is known to transactivate IFN-γ-responsive genes including iNOS [56] and IL-12 [57]. Recently, Delgado *et al.* (2003) demonstrated in mouse microglia that vasoactive intestinal peptide inhibited IFN-γ-induced JAK/STAT1 activation through upregulation of the cAMP/PKA pathway [58]. Therefore, antidepressant induced upregulation of the cAMP/PKA pathway may mediate inhibitory effects of antidepressants on LPS or IFN-γ-evoked inflammatory transactivations in immune cells (Fig. **1**).

The manner in which *in vivo* anti-depressant treatment increases intracellular cAMP levels appears to be strait forward. Explicitly, it is believed that antidepressants increase synaptic levels of 5-HT and NA through inhibiting reuptake by their transporters on presynaptic neurons. Thus causes activation of their receptors which are coupled to G proteins that can regulate the cAMP system. Through G-protein activation of adenylate cyclase (i.e., through the activation of 5-HT or NA receptor subtypes positively coupled to adenylate cyclase), cAMP production is increased.

It remains unclear as to how antidepressants increase intracellular cAMP levels *in vitro*. Antidepressants may act on cells *in vitro* independently of monoamine receptors coupled to G proteins. A recent genetic study has shown that genes of phosphodiesterases (PDEs), which degrade cAMP, are associated with a susceptibility to major depression and to antidepressant treatment response [59]. Accordingly, antidepressants may directly affect PDE functions in cells and thus increase the intracellular cAMP *in vitro*. Alternatively, we can presume that antidepressants could have direct effects on G proteins.

Maes and colleagues hypothesized that the mechanism is related to the effect of antidepressants on the serotonergic system by 5HT influencing cytokine production [30, 60]. Obuchowicz *et al.* suggested that the mechanism might be nonspecific because antidepressants are potent inhibitors of sodium and calcium influx [61]. Further studies on this subject are clearly warranted.

POTENTIAL OF ANTIDEPRESSANTS AS PREVENTIVES AGAINST ALZHEIMER'S DISEASE

Dementia and major depression are frequently comorbid among elder people. There is enough evidence from epidemiologic and neuropsychologic studies that major depression is associated with AD, even though it is uncertain whether major depression represents an early sign of dementia or a risk factor for dementia (for review see [62]).

It is well established that inflammatory processes are closely associated with the pathogenesis of a broad spectrum of neurodegenerative diseases [63, 64]. In AD, senile plaque is one of the neuropathological hallmarks of AD and a site of inflammatory processes, as evidenced by the presence of degenerating neurons and numerous reactive microglia and astrocytes [65, 66]. A number of *in vitro* studies have shown that amyloid-β-activated microglia damage or kill neurons by the release of inflammatory mediators such as pro-inflammatory cytokines, nitric oxide and superoxide radicals [67-70]. Therefore, chronic inflammation may be involved in the pathogenesis of both major depression and dementia.

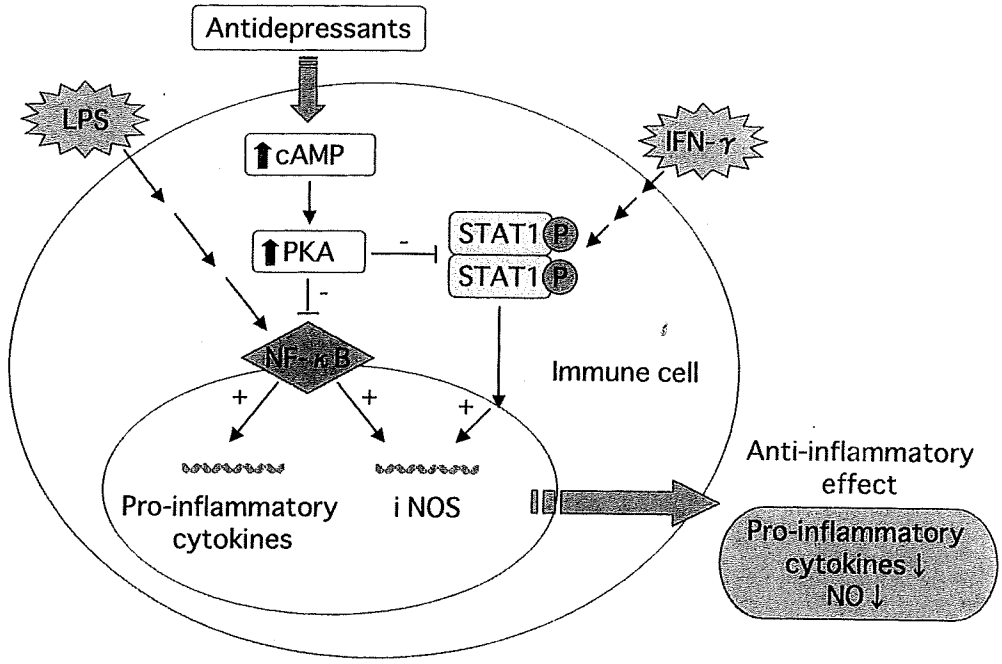

Fig. (1). Scheme for possible mechanism by which antidepressants exert anti-inflammatory effect in immune cells. Antidepressants may inhibit LPS or IFN-γ-evoked inflammatory transactivations through the up-regulation of cAMP/PKA pathway in immune cells. See text for details.

More than twenty epidemiological studies have shown that individuals are relatively spared from AD if they have been taking nonsteroidal anti-inflammatory drugs (NSAIDs) or have suffered from conditions where such drugs are routinely used (for review see [71]). In this regard, it is tempting to speculate that antidepressants with anti-inflammatory effects could be useful treatments for neurodegenerative diseases including AD. Interestingly, pre-symptomatic and chronic treatment with paroxetine has been shown to decrease AD-like pathology and reverse memory impairments in 3x transgenic AD mice [72]. Furthermore, in a small, 8-week double-blind placebo-controlled clinical study, fluoxetine was effective in reducing cognitive decline and behavioral abnormalities in patients with mild cognitive impairment [73]. This suggests that antidepressants could ameliorate AD or inhibit the progression of major depression to dementia.

It should be noted that such positive effects of antidepressants on memory and cognitive impairment might not be due to anti-inflammatory effects. Experimental evidence shows that chronic treatment with various antidepressants enhances neurogenesis in adult hippocampus [74, 75]. Clinical evidence indicates that long-term paroxetine treatment increases memory and hippocampal volume in patients with post traumatic stress disorder [76]. Accordingly, improvement of memory and cognition in the aforementioned two studies might be due to the hippocampal neurogenesis induced by antidepressants. Nevertheless, the anti-inflammatory properties of antidepressants may still be involved since the inflammation associated with LPS-activated microglia has been demonstrated to suppress hippocampal neurogenesis in adult rats [77].

CONCLUSIONS

Accumulating evidence indicates that major depression is associated with inflammation and that various types of antidepressants possess anti-inflammatory properties even though the exact mechanisms remain to be elucidated. Association between major depression and neurodegenerative diseases including AD may be based on the importance of chronic inflammation in the pathogenesis. Some preliminary studies support the hypothesis that antidepressants could prevent AD or inhibit the progression of major depression to dementia. Further studies along these lines are clearly warranted, even though careful consideration of the side effects of antidepressants is required in studies on aged people.

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Short Communication

Attenuated prefrontal activation during a verbal fluency task in remitted major depression

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The aim of the present study was to investigate whether a functional abnormality in the left prefrontal cortex observed in patients with major depression performing a verbal fluency task is present after remission of depression. Functional magnetic resonance imaging was used to study changes in cerebral blood oxygenation in eight remitted patients with major depression and 10 healthy control subjects during a verbal fluency task. Compared to the control subjects, the patients had a reduced response in the left prefrontal cortex (middle frontal gyrus, Brodmann area 10). These findings suggest the presence of dysfunction in the left prefrontal cortex during remission in major depression.

Key words: anterior cingulate cortex, depression, magnetic resonance imaging, prefrontal cortex, remission.

IMPAIRED COGNITIVE FUNCTION is a common and disabling feature of depression, both during an acute depressive episode and in the remitted state. A number of studies in recent years have used functional magnetic resonance imaging (fMRI) to study brain activation associated with cognitive activity in patients with depression. Although these studies have provided conflicting results due to the fact that most studies have used different cognitive tasks,[1–6] we reported previously that depressed patients showed significantly attenuated activations in the left prefrontal cortex (PFC) during a verbal fluency task, when compared to control subjects.[7] In the present study we used the same activation paradigm to investigate changes in brain activation in remitted patients with major depression.

METHODS

The study participants were eight remitted patients with major depression (six men, two women, aged 35–55 years) and 10 healthy volunteers (eight men, two women, aged 34–57 years) with no history of neurological or psychiatric illness. All subjects were right-handed according to the Edinburgh Handedness Inventory. All of the patients were inpatients at Hiroshima University Medical Hospital, diagnosed by three experienced clinicians as having major depressive disorder, but no other major disorders according to DSM-IV criteria.[8] Remission was defined as ≤7 on the 17-item Hamilton Rating Scale for Depression (HRSD).[9] Their mean score on the HRSD was 5.3 ± 1.4. The duration of the remitted phase in the patients prior to the study was 8.4 ± 3.3 days. All were medicated as follows: four patients were taking 200 mg fluvoxamine, and the other four were taking either 50 mg fluvoxamine, 150 mg clomipramine, 225 mg amoxapine, or 20 mg paroxetine. Seven of

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the patients and all of the healthy volunteers participated in the previous study.[7] The examinations were conducted under a protocol approved by the Ethics Committee of Hiroshima University School of Medicine. After complete description of the study to the subjects, written informed consent was obtained.

The verbal fluency activation paradigm, echo planar imaging acquisition, image processing, measurements of verbal fluency test performance, and data analysis were performed according to methods described previously.[7]

RESULTS

No significant differences were detected between the patients and the control subjects for verbal fluency performance (patients: mean, 21.8 ± 3.7 words; control subjects: mean, 25.8 ± 8.3 words; $P = 0.220$).

For both groups, verbal fluency task resulted in the significant activation of the left PFC ($P < 0.001$ uncorrected on the single voxel level and $P < 0.05$ corrected on the cluster level; Fig. 1a,b). The control group also had significant activation in the cingulate cortex and thalamus, while the depressed group did not ($P < 0.001$ uncorrected on the single voxel level and $P < 0.05$ corrected on the cluster level; Fig. 1a,b). A direct comparison on two-sample *t*-test at each voxel of the brain activation in the two groups showed that the control group had significantly greater activations than the patients in a small portion of the left PFC (middle frontal gyrus, Brodmann area 10; $P < 0.001$ uncorrected on the single voxel level, extent threshold of 10 voxels; Fig. 1c).

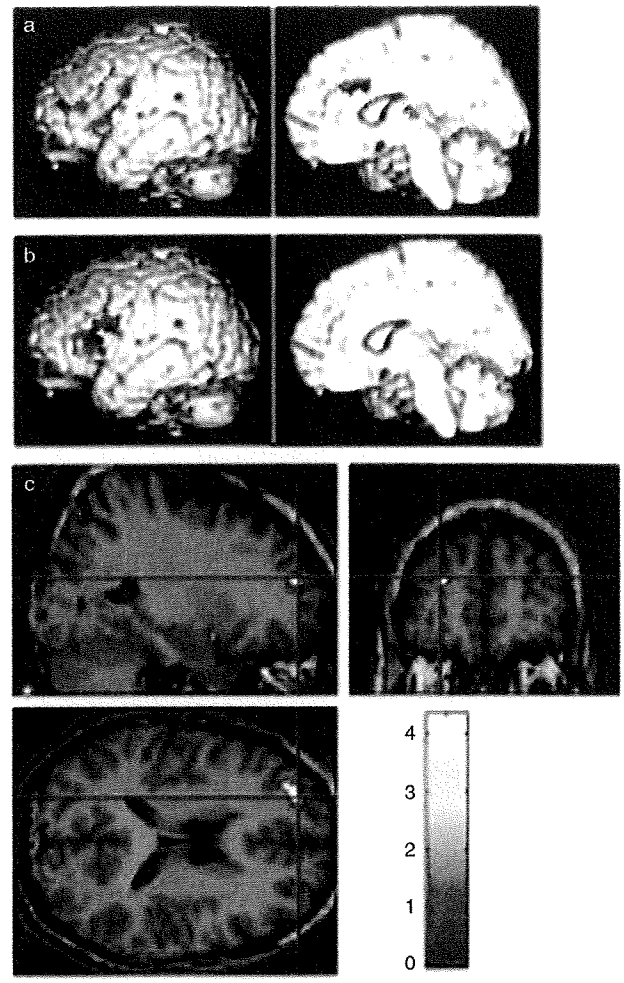

Figure 1. (a) Statistical parametric maps of brain regions (second-level analysis for 10 control subjects) showing significant activation associated with the verbal fluency task. (b) Statistical parametric maps of brain regions (second-level analysis for eight remitted patients with major depression) showing significant activation associated with the verbal fluency task. (c) Statistical parametric maps of brain regions in which 10 controls had significantly greater activation in a verbal fluency task than eight remitted patients with major depression. T-levels of activation are color-coded from red to yellow.

DISCUSSION

Within this verbal fluency neural network, brain activation in the left PFC remained impaired in patients in remission during the short observation period in spite of their clear clinical improvement. In our previous study there was no significant difference in this area of activation between depressive patients in recovery (defined as maintaining a score of ≤7 on the 17-item HRSD for >3 months) and healthy volunteers.[10] This result suggests that the brain activity may take longer to return to a normal level than the observed mood improvement.

Results of recent studies suggest that functional neuroimaging is a more sensitive assay of cognitive processing than behavioral measures.[11] Therefore, the neurophysiological problems identified in the present study may reflect subtle cognitive deficits of remitted patients. The present findings, however, are limited by the relatively small group size and potential medication effects. A second limitation is the short period of the remitted phase in the present patients. Although they were asymptomatic at examination, they fulfilled criteria for partial remission on

DSM-IV-TR. Further longitudinal studies using larger numbers of unmedicated subjects are required to elucidate the neurophysiological abnormalities in major depression.

ACKNOWLEDGMENTS

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ORIGINAL RESEARCH

Imaging-Pathologic Correlation in Corticobasal Degeneration

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BACKGROUND AND PURPOSE: The clinical diagnosis of corticobasal degeneration (CBD) is often difficult due to varied clinical manifestations. In 4 patients with neuropathologically confirmed CBD, characteristic imaging findings and correlations with neuropathologic features were evaluated. Furthermore, imaging findings in CBD were compared with neuropathologically confirmed progressive supranuclear palsy (PSP) for a differential diagnosis.

MATERIALS AND METHODS: Four patients with neuropathologically confirmed CBD were studied. We evaluated the area of the tegmentum in the midsagittal plane, subcortical white matter (SCWM) abnormality, asymmetric cerebral atrophy, and signal-intensity abnormality in the subthalamic nuclei on MR imaging and compared them with histopathologic findings. Then, MR imaging findings in CBD were compared with those in 13 patients with PSP.

RESULTS: On MR imaging, 3 patients had asymmetric cerebral atrophy extending to the central sulcus. On midsagittal sections, the mean midbrain tegmentum area was 66 mm^2, being markedly smaller than normal, but there was no significant difference between PSP and CBD. All patients had signal-intensity abnormalities of the SCWM, constituting primary degeneration neuropathologically; however, no diffuse signal-intensity abnormality in the SCWM existed in the 13 patients with PSP. In 3 patients, T1-weighted images showed symmetric high signal intensity in the subthalamic nuclei. Neuropathologically, these areas showed characteristic CBD. MR imaging signal-intensity changes also existed in 4 patients with PSP; however, subthalamic nucleus degeneration was more severe in PSP than in CBD.

CONCLUSIONS: In cases with midbrain tegmentum atrophy and signal-intensity changes in the subthalamic nuclei, the differential diagnosis distinguishing CBD from PSP based on MR imaging alone was difficult. White matter lesions and asymmetric atrophy can be useful for a differential diagnosis.

Corticobasal degeneration (CBD) is a slowly progressive disorder with a clinically asymmetric onset characterized by apraxia, dystonia, postural instability, and an akinetic-rigid syndrome that does not respond to levodopa. However, clinical phenotypes of Alzheimer disease, Pick disease, and progressive supranuclear palsy (PSP) with similar characteristic features often make a differential diagnosis distinguishing these entities from CBD difficult in clinical practice.

Koyama et al[1] recently reported asymmetric cerebral atrophy with dominance contralateral to the more clinically affected side, hyperintensity in the subcortical white matter (SCWM) in the frontotemporal area on fluid-attenuated inversion recovery (FLAIR), and atrophy of the midbrain tegmentum as new imaging findings of clinically diagnosed CBD, but no imaging findings in pathologically proved cases have been reported.[3,4] We encountered 4 patients with neuropathologically confirmed CBD in whom the findings could be compared with those of MR imaging. Cortical symptoms were unclear in 3, and it was difficult to make a diagnosis on the basis of clinical symptoms alone because of underlying dementia. Although the number of cases was small, because the neuropathology and images were collated in all cases, this study was significant with regard to the objectivity of the imaging findings associated with an accurate diagnosis. We also thought that it was important to identify differences in imaging findings between CBD and PSP, in which severe atrophy of the midbrain tegmentum has been reported.[1,2] Therefore, MR imaging findings in CBD were compared with those in 13 cases of neuropathologically confirmed PSP.

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Materials and Methods

Patients

Four patients (1 man, 3 women) with neuropathologically confirmed CBD were evaluated retrospectively. The patients' mean age at death was 70.8 years (range, 67–74 years). Table 1 lists the patient characteristics. The MR imaging findings in the patients with CBD (Table 2) were compared with those in 13 patients with neuropathologically confirmed PSP. All 13 patients with PSP were men, with a mean age at death of 78.3 years (range, 64–87 years). For the comparative evaluation of atrophy of the midbrain tegmentum, 10 aged-matched control subjects (4 men and 6 women) with no neuropathologic degenerative disease or cerebrovascular disorder were selected (mean age at death, 74.6 years; range, 68–83 years).

MR Imaging Examinations

All studies were performed with a 1.5T MR imaging unit (Signa Excite HD; GE Healthcare, Milwaukee, Wis). Axial T2-weighted images (TR/TE, 4300/89 ms; NEX, 2; FOV, 220 mm; section thickness, 5 mm with a section gap of 1 mm) and FLAIR images (TR/TE, 10,002/106 ms; TI, 2500 ms; NEX, 1; section thickness, 5 mm with a gap of 1 mm), sagittal T1-weighted images (TR/TE, 600/14 ms; NEX, 2; section thickness, 5 mm with a gap of 1 mm), or sagittal spoiled gradient-echo

Table 1: Clinical findings of pathologically confirmed corticobasal degeneration

Case No.	Age at Onset (yr)	Sex	Duration (yr)	Rigidity	Dystonia	Pyramidal Signs	Cortical Dysfunction	Vertical Gaze Palsy	Dementia	CDx
1	74	F	10	Lt>Rt	–	–	Ocular apraxia	+	Mute	PSP?
2	68	F	6	Lt>Rt			Apraxia (Lt hand)	±	+ Severe akinetic mute	AD
3	67	M	3	Rt>Lt			No cortical sign	+	+ Severe	PDD
4	74	F	6	Rt>Lt	–	–	–	+	+ Severe	CBD

Note:—CBD indicates corticobasal degeneration; PSP?, progressive supranuclear palsy suspected; CDx, clinical diagnosis; AD, Alzheimer disease; PDD, Parkinson disease with dementia; –, no symptom; +, obvious symptom; ±, suspicious symptom; Lt, left; Rt, right.

Table 2: MR imaging findings of neuropathologically confirmed corticobasal degeneration

Case No.	Atrophy (Dominant Cerebral Hemisphere)	White Matter Hyperintensity on FLAIR		Hyperintensity on T1WI in Bil Subthalamic Nucleus
		Precentral Gyrus	Frontal Lobe	
1	Rt frontal operculum and convexity	–	+	+
2	Bil frontal convexity	–	+	+
3	Lt frontoparietal	Bil	+	+
4	Rt frontoparietal	Rt	+	+

Note:—FLAIR indicates fluid-attenuated inversion recovery; T1WI = T1-weighted imaging; Bil, bilateral; –, no signal abnormality; +, obvious signal abnormality.

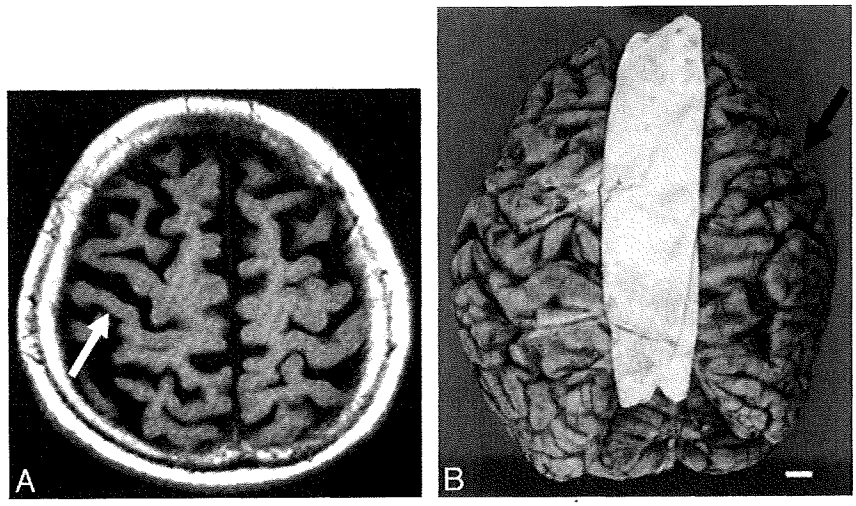

Fig 1. Corticobasal degeneration, case 1. An 84-year-old woman. *A*, Axial T2-weighted image shows right-side-dominant atrophy including the central sulcus (*arrow*). *B*, A macrospecimen of this patient shows right-frontal-dominant atrophy (*arrow*).

images (TR/TE, 21/6 ms; TI, 0 ms; flip angle, 20°) were obtained in all patients with CBD and PSP and healthy controls. Spin-echo coronal T1-weighted images (TR/TE, 600/14 ms; NEX, 2; section thickness, 5 mm with a gap of 1 mm) were obtained in 3 of the 4 patients with CBD, 7 of the 13 patients with PSP, and the 10 age-matched healthy controls. In 1 patient with CBD and 3 with PSP, T1-weighted coronal spin-echo images could not be obtained; spoiled gradient-echo imaging (TR/TE, 21/6 ms; TI, 0 ms; flip angle, 20°) was selected instead. These patients and 3 other patients with PSP without coronal sections were excluded from evaluation of the T1-weighted signal intensity. The area of the midbrain tegmentum was measured on an MR imaging workstation by using the method of Oba et al[2] in a T1-weighted midsagittal section through the center of the interpeduncular cistern and the center of the cerebral aqueduct. Two neuroradiologists (A.M.T. and M.T.) performed these measurements blindly, twice at different times.

The localization and laterality of cerebral atrophy, signal intensity in the subthalamic nuclei, and signals in the SCWM were only qualitatively investigated because of the limitations of the retrospective nature of pathologically confirmed cases. The 2 neuroradiologists blindly investigated images of 4 patients with CBD, 13 patients with PSP, and 10 healthy controls twice at different times and visually evaluated the following points: 1) the presence or absence and laterality of cerebral atrophy and whether the atrophy included the central sulcus on T1-weighted imaging, 2) the presence or absence and localization of a high signal intensity in the SCWM on T2-weighted or FLAIR imaging, and 3) the presence or absence of an increase in the signal intensity in the subthalamic nuclei in the coronary view on T1-weighted imaging.

Neuropathologic Examinations

Informed consent for autopsy was obtained from all of the patients or their families. All serial autopsy cases were examined with the Brain Bank Aging Research protocol, irrespective of clinical diagnosis.[3] At autopsy, after taking photographs of the whole brain, we serially sectioned the nondominant hemisphere or the hemisphere spared from focal lesions at a 7-mm thickness. The cerebrum was cut on the coronal plane; the brain stem, on the axial plane; and the cerebellum, on

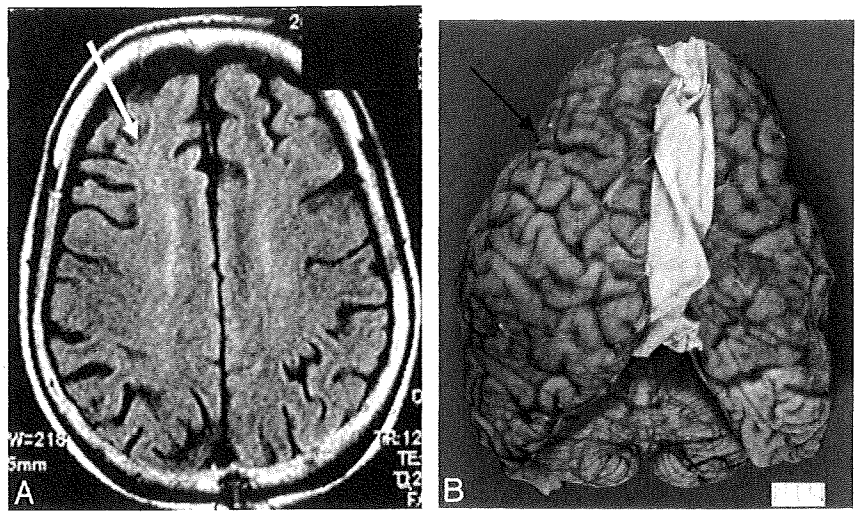

Fig 2. Corticobasal degeneration, case 2. A 74-year-old woman. *A*, An axial fluid-attenuated inversion recovery image 3 years before autopsy shows no obvious asymmetric atrophy. Subcortical hyperintensity is shown in the right frontal white matter (*white arrow*). *B*, A macrospecimen of this patient shows mild frontal atrophy with some asymmetry (*arrow*).

the sagittal plane. Photographs were taken of all sections. Small pieces of the anterior amygdala; posterior hippocampus; frontal, temporal, and occipital poles; supramarginal gyrus; and rostral midbrain were directly fixed in 4% paraformaldehyde for 48 hours and prepared for immunohistochemical and ultrastructural studies. The remaining sections were quick frozen and stored at −80°C. The hemisphere kept for morphologic examinations was fixed in 20% neutral buffered formalin for 7–13 days and cut into 7-mm-thick sections, similar to those in the contralateral hemisphere. Paraffin-embedded sections of representative areas of the brain were examined.

The selected anatomic structures included those recommended by the Consortium to Establish a Registry for Alzheimer Disease,[4] the Consensus Guidelines for the Diagnosis of Dementia with Lewy Bodies,[5,6] Braak and Braak's recommendation,[7] and the Diagnostic Criteria of Corticobasal Degeneration and Progressive Supranuclear Palsy.[8,9] These included the frontal pole; temporal pole; cingulate gyrus; second frontal gyrus; accumbens and septal nuclei; amygdala; basal nucleus of Meynert; second temporal gyrus; anterior hippocampus with entorhinal and transentorhinal cortices; basal ganglia and hypothalamus with mamillary bodies; subthalamic nucleus; posterior hippocampus; thalamus with the red nucleus; motor cortex; parietal lobe with the intraparietal sulcus; visual cortex; midbrain; upper and middle pons; medulla oblongata; cerebellar vermis; dentate nucleus; and multiple cervical, thoracic, and lumbar levels of the spinal cord.

Six-micrometer-thick sections were routinely stained with hematoxylin-eosin and the Klüver-Barrera method. Selected sections were stained with the modified methenamine, Gallyas-Braak, and Bielschowsky silver staining for age-related changes, with Congo red for amyloid β deposition and elastica-Masson trichrome staining for vascular changes.

Immunohistochemistry

Six-micrometer-thick serial sections were immunohistochemically stained by using a 20NX autostainer (Ventana, Tucson, Ariz), as previously described. The antibodies applied to all the cases were the following: antiphosphorylated α-synuclein (psyn); phosphorylated tau (ptau) (AT8, monoclonal; Innogenetic, Temse, Belgium); 3-repeat tau (RD3, amino acids 209–224, monoclonal, Upstate; Millipore, Lake Placid, NY); 4-repeat tau (RD4, amino acid 275–291, monoclonal, Upstate; Millipore); amyloid β 11–28 (12B2, monoclonal; IBL, Maebashi, Japan); glial fibrillary acidic protein (polyclonal; DAKO, Glostrup, Denmark); HLA-DR (monoclonal, CD68; DAKO); phosphorylated neurofilament (monoclonal SMI31; Sternberger Immunochemical, Baltimore, Md); myelin basic proteins (polyclonal, DAKO); and ubiquitin (polyclonal, DAKO) antibodies.

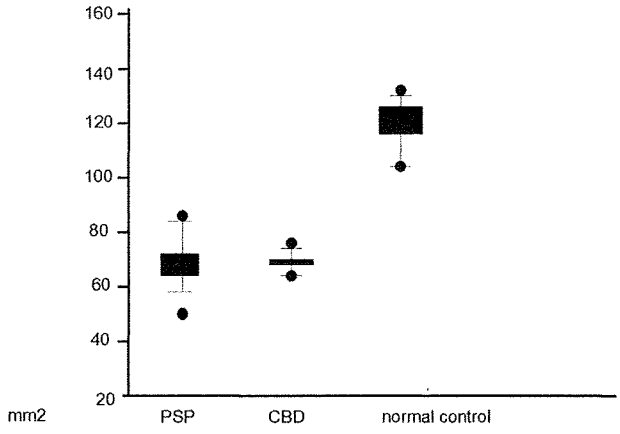

Fig 3. Scatterplot (mean, SD, and range) of the area of the midbrain in patients with progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and age-matched healthy controls. There was no individual overlap of the midbrain tegmental area between the healthy controls and patients with CBD and PSP, apparently showing that severe atrophy of the midbrain tegmentum was present in patients with CBD and PSP.

In addition to the routine neuropathologic examination mentioned above, studies were performed at sites of MR imaging signal-intensity abnormalities or atrophy to correlate the radiologic and pathologic findings. To compare them with MR imaging findings, 2 neuropathologists investigated the following points in addition to routine examinations: 1) the macroscopic presence or absence, laterality, and localization of cerebral atrophy at the time of sectioning the brain and after fixation, 2) the macroscopic presence or absence of atrophy of the midbrain tegmentum at the time of sectioning the brain and after fixation, 3) the presence or absence and degree of degeneration of the subthalamic nuclei, and 4) the presence or absence of a lesion in the SCWM and whether the lesion constituted primary or secondary degeneration in CBD. For brain samples, 7-mm coronal sections of the lateral region passing the mamillary body vertical to the hippocampal structure were prepared. Abnormal intensi-

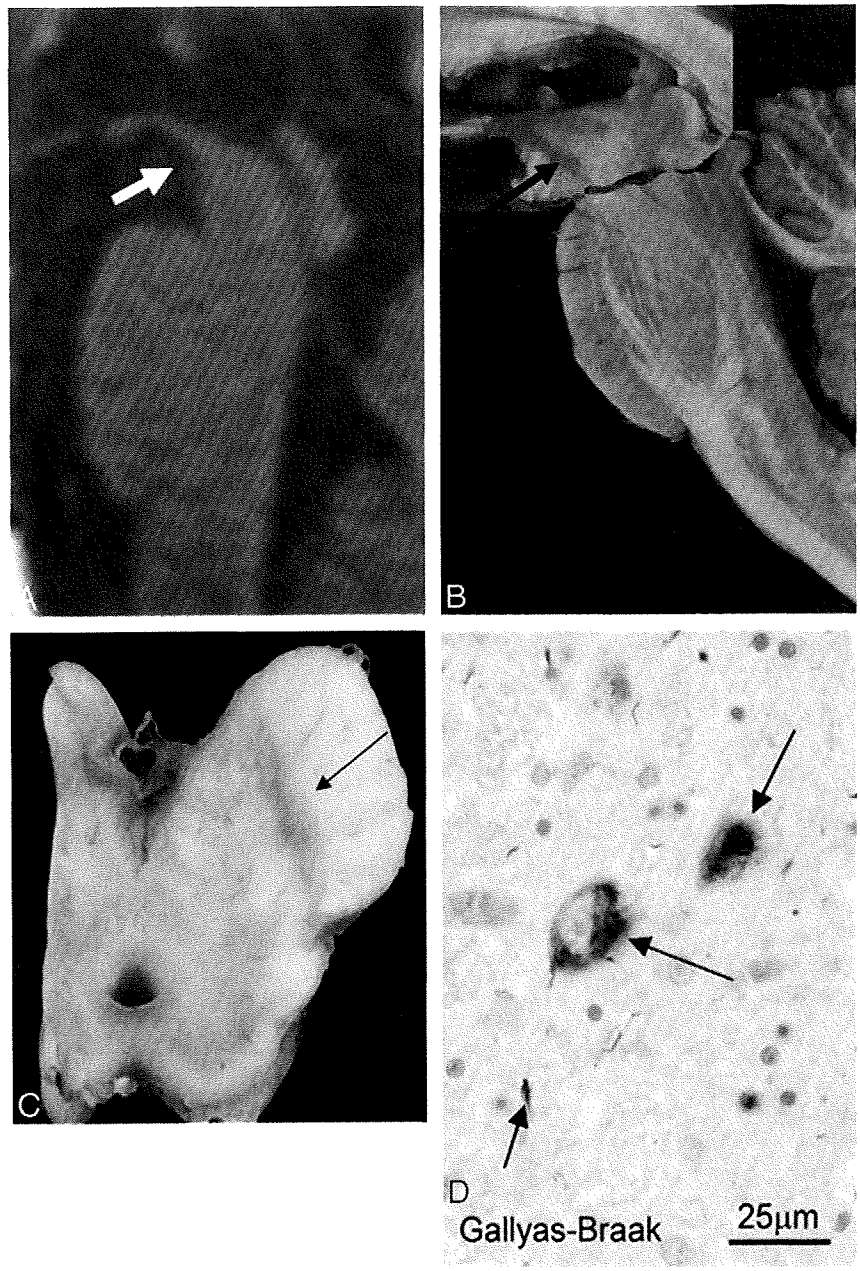

Fig 4. Corticobasal degeneration (CBD), case 1. An 84-year-old woman. *A*, T1-weighted midsagittal image clearly shows atrophy of the midbrain tegmentum (*arrow*). The area of the midbrain tegmentum is 73 mm^2. *B*, A macroscopic specimen of the midbrain shows marked atrophy (*arrow*). *C*, A macroscopic view of the midbrain shows discoloration of the substantia nigra (*arrow*). *D*, A microscopic view of the substantia nigra (Gallyas-Braak stain) shows argyrophilic threads and granular or fibrous inclusion bodies (*arrows*). These are consistent with CBD.

ties on MR imaging were collated with the pathologic preparations as accurately as possible, with the line passing the mamillary body vertical to the hippocampal structure as the baseline, and new pathologic sections were cut out as needed.

Results

Asymmetric Cerebral Atrophy

Asymmetric cerebral atrophy was observed in 3 of 4 patients with predominance contralateral to the more clinically affected side. In all 3 patients, cerebral atrophy affected the area including the central sulcus. In 1 patient, the radiologic and pathologic findings of predominantly frontal lobe atrophy were correlated (case 1, Fig 1*A*, -*B*). In 1 patient (case 2, Fig 2*A*, -*B*) in whom the interval between MR imaging and autopsy was 3 years, asymmetric cortical atrophy was difficult to detect on MR imaging, but frontal atrophy with some asymmetry was seen on autopsy. In this patient, clinical evaluation revealed no asymmetric cortical symptoms, so the clinical diagnosis was Alzheimer disease. In the 13 cases with PSP, excluding 1 patient, no asymmetric atrophy was noted.

Atrophy of Midbrain Tegmentum

On midsagittal sections, by using the method of Oba et al,[2] the mean area of the midbrain tegmentum of the 4 patients with CBD was 67.6 ± 7.4 mm^2 (range, 62.3–73.3 mm^2) (Fig 3; case 1, Fig 4*A*–*D*), which is markedly less than normal, with the

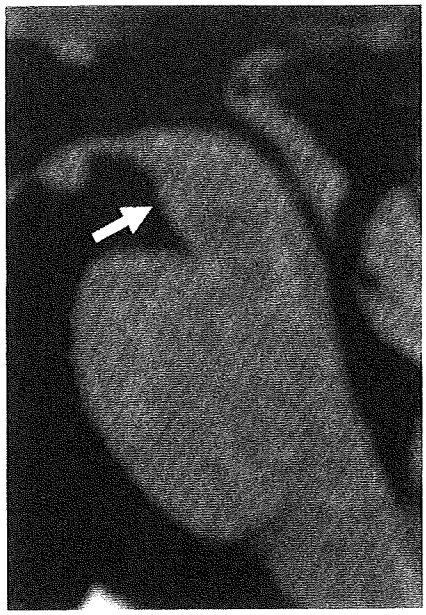

Fig 5. An age-matched healthy control 72-year-old woman. T1-weighted midsagittal image shows no obvious atrophy of the midbrain tegmentum (*arrow*). The area of the midbrain tegmentum is 128 mm^2.

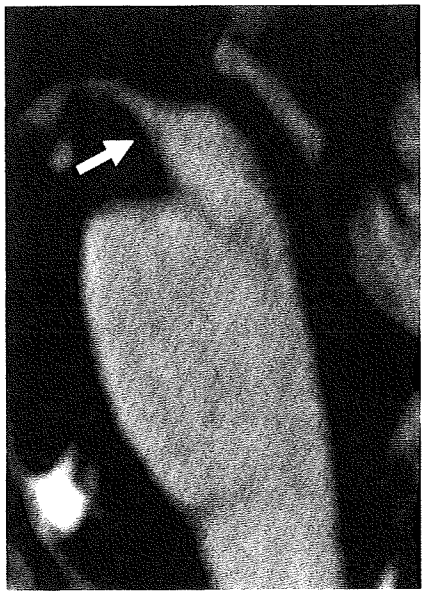

Fig 6. Progressive supranuclear palsy. A 74-year-old man. T1-weighted midsagittal image clearly shows atrophy of the midbrain tegmentum (*arrow*). The area of the midbrain tegmentum is 71 mm^2.

mean area of 123.8 ± 10.8 mm^2 in the controls (range, 108.0–132.4 mm^2) (Figs 3 and 5). In the 13 patients with neuropathologically confirmed PSP, the mean area was 70.7 ± 12.1 mm^2 (range, 58.6–89.8 mm^2) (Figs 3 and 6). Although statistical analysis was not possible because of the small number of cases, there was no individual overlap of the midbrain tegmental area between the healthy controls and patients with CBD and PSP, apparently showing that severe atrophy of the midbrain tegmentum was present in CBD and PSP. On neuropathologic examination, there was also atrophy of the midbrain tegmentum and marked depigmentation of the substantia nigra and locus ceruleus. Other findings included melanophagia and gliosis, and Gallyas-Braak silver staining revealed argyrophilic threads and granular or fibrous inclusion bodies. These findings were consistent with CBD. In the pontine tegmentum and oculomotor and trochlear nuclei, many AT8-immunoreactive pretangles were observed.

SCWM Signa-Intensity Change on T2-Weighted Images and FLAIR

In all 4 patients with CBD, T2-weighted images and FLAIR showed diffuse high-intensity signals in the SCWM. In 3 patients, high signal intensity in the SCWM was recognized on the predominantly atrophic side (case 1, Fig 7*A*–*C*). In 1 patient, a high signal intensity was noted bilaterally over a wide area in the frontal lobes (case 3, Fig. 8*A*–*C*). Corresponding to the sites of white matter lesions, myelin sheath staining was decreased, and these sites were stained positively for antiphosphorylated tau antibody. These changes are primary characteristic of CBD. On neuropathologic examination, there was some involvement of U-fibers, but because of image-quality limitations on MR imaging, U-fiber involvement could not be specifically detected. In the 13 patients with PSP, there was no diffuse signal-intensity abnormality in the SCWM. There was no neuropathologic finding indicating primary degeneration of the SCWM.

Symmetric High Signal Intensity Bilaterally in Subthalamic Nuclei on T1-Weighted Images

T1-weighted MR images showed symmetric high signal intensity bilaterally in the subthalamic nuclei in all 3 patients in whom T1-weighted images were obtained (case 1, Fig 9*A*–*C*). In the remaining patient, the signal intensity in the subthalamic nuclei was not evaluated because no T1-weighted coronal spin-echo images could be obtained. Spoiled gradient echo (TR/TE, 21/6 ms; TI, 0 ms; flip angle, 20°) was selected instead. These sites showed a brownish change on macroscopic examination, and on microscopic examination, antiphosphorylated tau antibody–positive neurons and gliosis were observed. These changes were characteristic of CBD. MR imaging signal-intensity changes were also present in 4 of 7 patients with PSP in whom T1-weighted images were obtained (Fig 10*A*–*C*). Because neuropathologically examined cases were retrospectively evaluated, signal-intensity evaluation was limited to visual examination by 2 neuroradiologists. It was difficult to distinguish CBD and PSP on imaging, and no asymmetry was identified. However, on neuropathologic examination, degeneration of the subthalamic nuclei was more severe in PSP than in CBD.

Discussion

In 3 of the 4 patients with CBD, atrophy was predominantly contralateral and extended to the central sulcus. On neuropathologic examination, the MR imaging findings of atrophy were confirmed. In 1 patient with no asymmetric cortical symptoms, there was no asymmetry on MR imaging (case 2, Fig 3*A*, -*B*) and the clinical diagnosis was Alzheimer disease. In this patient, in whom the interval between the last MR imaging and autopsy was 3 years, neuropathologic examination did show asymmetric atrophy, but it was mild compared with that in the other 3 patients. In some patients, CBD presents with dementia, behavioral abnormalities, and attention deficit in